REMARKS AND ARGUMENTS

Status of claims:

As listed above in the Listing of Claims, of the original 41 claims, claims 24-41 are withdrawn as non-elected claims, and of the remaining claims, claim 12 is cancelled and claims 1, 3, 7, 9, 11, 13, 14 , 18 and 23 are currently amended. Further, in view of the above amendments and following remarks, Applicant believes that all issues have been addressed appropriately and diligently. Accordingly, Applicant requests allowance of all the currently examined claims.

1. Information Disclosure Statement

Applicants have submitted an Information Disclosure Statement containing related references for this invention on January 30, 2006. Of course the Applicants will continue to forward additional related references if and when they become aware of such refernces.

2. Amino Acid/Nucleotide Sequences

As requested in the Office Action dated November 21, 2005, Applicants electronically submitted a CRF and a Statement regarding Identity of CRF for the Sequences SEQ ID No. 1 and SEQ ID No. 2 on December 21, 2005. No new matter was introduced in the Sequence Listings.

3. Use of registered trademarks

In the Action it was noted that the trademark ADOBE PHOTOSHOP® was inappropriately used in paragraph [0188]. To that effect, Applicant regrets any lack of clarity, since the trademark was used depicting the mark "Adobe Photoshop" with the generic term

"software" describing the product. In order to further clarify, however, Applicant has amended the specification to include the terms ADOBE PHOTOSHOP® in all caps, followed by the generic term "graphics software"

4. Drawings

In the Action, Figures 1.2, 4.2 and 6.2 were objected to since portions of the text were found unreadable. Accordingly replacement figures are provided for enhancing clarity of the original drawings. The replacement drawings are appended at the end of this response. No new matter has been introduced in the replacement drawings.

5. Claim objections

Applicants thank the Examiner for providing guidance for improving syntax and grammar of the claims. As per Examiner's observations, amendments in syntax and grammar have been made in claims 3, 9, 11, 13. These amendments are for clarity purposes only and do not alter the scope of the claims.

6. Claim rejections under 35 U.S.C 112, first paragraph

In the Action, claim 18 was rejected based on 35 U.S.C 112, first paragraph as failing to comply with written description requirements. Per the Action, the claim allegedly contained subject matter which was not described in the specification. The subject matter at issue was "a partially curved affinity substrate." For the following reasons Applicant respectfully disagrees with this rejection and requests reconsideration of claim 18.

First, Applicant directs the Office to Figure 9 and a preferred embodiment described in paragraphs [0025], [0028], [0046] and [0173]-[0176]. As described herein, the inventors

observed differences of ±20° between the apparent direction of contact of the stamp with the surface and the azimuthal orientation of the Liquid Crystal. To better control the direction of contact of the stamp with the surface and thus test its role in dictating the observed azimuthal alignment of the Liquid Crystal, the inventors adopted the use of a cylindrical stamp (Figure 9). Thus, in an exemplary embodiment as described in Example 8 of the specification, cylindrical stamps were exploited to define the azimuthal molecular-level organization of the patterned species. In this Example, the inventors observed differences of ±20° between the apparent direction of contact of the stamp with the surface and the azimuthal orientation of the Liquid Crystal.

Second, a cylinder is a partially curved three-dimensional object, which is defined by "the surface traced by a straight line moving parallel to a fixed straight line and intersecting a fixed planar closed curve," or the space bounded by a cylinder and two parallel planes cutting all its elements," the see Merriam-Webster Online Dictionary. Therefore, a cylindrical affinity substrate encompasses a partially curved substrate as claimed. Based on the exemplary embodiment described in the specification, Figure 9 and the arguments above Applicant has provided sufficient and necessary written description for claim 18. Of course, the above described exemplary embodiment describes a cylindrical stamp, however, one of ordinary skill in the art may also provide other partially curved substrates such as an ellipsoid (3-dimensional ellipse), a hemisphere (3-dimensional semicircle) or similar 3-dimensioned arcuate surfaces to achieve similar azimuthal orientation of the liquid crystal.

Accordingly, Applicant requests reconsideration of the written description rejection of claim 18.

7. Claim rejections under 35 USC 112, second paragraph

In the Action, Claims 1-23 were rejected under 35 USC 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. At issue were the following terms and phrases:

(a) Inking and Stamping

Applicant has deleted references to the terms inking and stamping for clarification purposes only. As one of ordinary skill in the art would however, understand the terms, the step of "inking" refers to step (a) of claim 1, i.e., contacting a sample having or suspected of having a ligand with an affinity substrate and the term "stamping" refers to step (b) of claim 1, i.e., contacting the affinity substrate with a detection surface.

(b) The ligand which is bound to the receptor

In the Action, it was noted that claim 1 did not recite the step in which the ligand is bound to the receptor. Accordingly, Applicant has amended the claim for clarity purposes to explain the step that when the sample contains the ligand of interest, the receptor of the affinity substrate specially binds to it.

(c) Detecting presence of the ligand on the detection surface

Applicant has amended claim 1 to clarify how detection of a ligand occurs on the detection surface. As described in several exemplary embodiments, see for example paragraphs [0061], [0106], [0107], the presence of the ligand may be generally detected visually by placing a liquid crystal on the detection surface. In the other embodiments of the invention, the detection surfaces can also be covered with a liquid crystal, typically between 1 micrometer and 100 micrometers thick that can be deposited on the detection surface and can be used without the use of a second substrate. In some embodiments, the liquid crystal can be thermally annealed after

contact with the detection substrate in order to maximize the response of the liquid crystal to the presence of the ligand on the substrate. Also, the liquid crystal may be detected optically or electrically. Examples of detection surfaces suitable for use in the present invention are disclosed in U.S. Patent Application Publication Nos. US 2002/0004216, US 2002/0055093 and US 2003/0099993, which are incorporated in the application by reference.

(d) Further comprises a liquid crystal

In view of the clarification in claim 1, the use of a liquid crystal with the detection surface is clear and definite.

(e) Detection substrate

In view of the above clarification, the term "the detection substrate" has sufficient antecedent basis.

(f) Antibodies or functional fragments thereof

The primary methodology used in this invention for the detection of ligands is based on affinity binding of the ligand to the receptors in the affinity substrate. Accordingly, one of ordinary skill in the art may easily determine that the term "antibodies or functional fragments thereof" refers to any antibody fragment that remains operable for binding to the affinity substrate. Usage of the term "functional fragment is established in the art of receptor-ligand binding, for example see claims in recently issued US Patent 6,998,123. Further such fragments may be determined using routine wet experiments, or through routine-in-silico computer modeling.

Further in paragraph [0068] of the Application various examples of possible ligands are described, such as various suitable biomolecules and biomolecule recognition agents, including peptides and polypeptides; carbohydrates; toxins; metals, such as heavy metals; chelators; pathogens, including viruses and bacteria; nucleic acids, such as RNA and DNA, their analogs and mimics; biotin; avidin; sugars; antibodies; FAB and FAB' or other active fragments of antibodies such as, but not limited to, immunoglobulins, such as but not limited to, IgG; small organic molecules, e.g., drugs, chemical agents, pesticides, herbicides and the like. Immunoglobulins including IgG, IgA, IgM, IgD, and IgE, and fragments of immunoglobulins are preferred receptors, and IgG and fragments of IgG are especially preferred receptors. Examples of biomolecules and ligands that can be used in the present invention are also discussed in U.S. Patent Nos. 6,171,802 and 6,284,197, which are incorporated by reference in the Application. Applicant therefore believes that the term "functional fragment thereof" is clear and definite.

(g) Nucleic acid analogs or mimic

Nucleic acid analogs and mimics are terms of art, well known to one of ordinary skill in the art. Several analogs and mimics are described in literature and various patents, for example see US Patents 5,637,683, 6,451,530 and 5,705,333. Accordingly applicant believes that these terms are clear and definite.

(h) A functional fragment thereof

As described above, the primary methodology used in this invention for the detection of ligands is based on affinity binding of the ligand to the receptors in the affinity substrate. Accordingly, one of ordinary skill in the art may easily determine that the term "a functional fragment thereof" refers to any molecular fragment that remains operable/functional for binding

to the affinity substrate. Use of fragments, instead of whole molecules is well established in the art of ligand detection. As an example, it is well established in the art to use fragments of biomolecules, organic molecules, herbicides, pesticides, etc. to detect the presence of these molecules. Thus, for example, several commercial products exist for the detection of biomolecular fragments such as endotoxins. The Applicant believes, the use of the terms "functional fragment thereof" is therefore clear and definite, especially in view of the state of the art in this related field.

(i) Peptide-terminated

In certain exemplary illustrations peptide-terminated PDMS is provided in the specification as filed. Applicant directs attention specifically to Examples 11 and 12, which teach methodology for the preparation and use of peptide terminated PDMS stamp. Example 11 specifically teaches cysteine terminated PDMS stamp, see paragraphs [0193]-[0196], and Example 12 specifically teaches capture and release of target anti-pY antibody using peptide modified stamps. Further, as discussed in paragraph [0195]-[0196], the PDMS stamp is treated with BSA. The covalently attached BSA has free amine groups from lysine residues not in contact with the stamp. Therefore these free amines could be used to attach peptide molecules via a heterobifunctional linker. Overall, since the PDMS stamp itself is peptide terminated, the term "peptide terminated," especially in view of the specification is clear and definite.

(j) Capable of detecting

Once the peptide terminated or antibody-terminated PDMS Stamp binds to the phosphorylated peptide or protein respectively, the detection surface is then capable of detecting

these ligands with a Liquid Crystal. However, for clarity, claims 7 and 9 have been amended to reflect the binding of the respective ligands on to the affinity substrate.

(k) Essential element

In view of the above clarification and amendments to claims 7 and 9, there are no essential elements missing from these claims.

(l) Antibody terminated PDMS.

Preparation and use of antibody-terminated PDMS stamps are described the specification, for example, in paragraph [0173]. Thus, in an exemplary embodiment described here, affinity stamps were prepared by the covalent attachment of biotinylated bovine serum albumin to the surface of a PDMS stamp (see Materials and Methods). Following incubation of an aqueous solution of anti-biotin IgG on the surface of the stamp, the surface of the stamp was rinsed with aqueous buffer and then contacted with a film of gold that was functionalized with $NH_2(CH_2)_2SH$. Further, the antibody terminated PDMS stamp is capable of binding to a protein, which is detectable with the aid of a liquid crystal. Detailed description of antibody terminated PDMS stamps is also provided in numerous paragraphs and examples throughout the specification. Accordingly use of the terms "antibody-terminated" is both clear and definite.

(m) Receptors have specificity for more than one ligand

As described in the specification, in an exemplary embodiment, and as shown in paragraph [0181] the microarrayer is used to create four arrays of 25 spots (5 spots per antibody). For example, to detect proteins phosphorylated at different residues, the following antibodies could be arrayed: pan-reactive 111.6 Ab (Lab Vision), and phosho-specific antibodies anti-

pY1068 (Biosource), anti-pY1086 (Biosource), anti-pY1148 (Biosource), and anti-pY1173 (Upstate). Accordingly in certain embodiments of the invention, the array of receptors may be envisioned to have a plurality of receptors wherein each receptor binds only to one ligand. Although, it is well established in the art to have multiple ligands capable of binding to the same receptor, for clarity purposes, the claim has been amended such that each receptor in the array binds to a single ligand. Further, in totality, since there is an array of receptors, the array will be capable of binding to multiple ligands, when each receptor binds to a single ligand.

(n) Various residues of EGFR

Following is paragraph [0181] of the specification:

> [Para 189] After curing overnight at 80°C, the PDMS is oxidized using an oxygen plasma (Plasma Etch PE-200, 8sccm, 20 seconds, 100W). The oxidized PDMS is functionalized with a primary amine by immersion in an aqueous solution containing 10% APES at 80°C for 1 hour. The surface is functionalized with a carboxylic acid by incubating in 0.1M Succinic Anhydride in DMF (12min), then rinsed with DMF and stored in PBS. The stamp is activated with NHS/EDC and rinsed with PBS. The stamp is taped to a glass microscope slide to attach to the GeneMachines OmniGrid Microarrayer. The Microarrayer is used to create **four arrays of 25 spots** (5 spots per antibody). For example, to **detect proteins phosphorylated at different residues, the following antibodies could be arrayed: pan-reactive 111.6 Ab (Lab Vision), and phosho-specific antibodies anti-pY1068 (Biosource), anti-pY1086 (Biosource), anti-pY1148 (Biosource), and anti-pY1173 (Upstate).** Glycerol (40%) is added to the antibody solutions to reduce evaporation of the droplet. The PDMS is deactivated with 1% BSA in PBS for 10 min. Small drops of WT (+ and – treatment with EGF) and PAR (+ and – treatment with EGF) membrane extracts are added onto the four antibody arrays separated by a silicon gasket or hydrophobic pen and incubated for 6 hours at 4°C. The stamp is rinsed with PBS with 0.01% Triton X-100, PBS, and water. The stamp is roller-printed onto 30° obliquely-deposited gold functionalized with an amine-terminated monolayer, as described in the preceeding example. The stamped protein is imaged by sandwiching 5CB between the obliquely-deposited gold substrate and an OTS-treated glass slide. Images are taken using a digital camera mounted onto a polarized light microscope. The luminosity of the 5 spots is averaged to give a quantitative characterization of total EGFR and phosphorylated EGFR of each of the membrane extracts.

This exemplary embodiment teaches the methodology for detecting ligands using affinity substrate, wherein the ligands to be detected are proteins phosphorylated at various residues of

the Epidermal Growth Factor Receptor, accordingly, applicant believes that the term various residues of EGFR is a clear and definite term. For clarity sake, Applicant has amended the term in claim 14. This amendment however does not alter the scope of the claim.

(o) Partially curved affinity substrate

Please see discussion of partially curved affinity substrate on pages 10 and 11 of this paper. Based on the above discussion the terms partially curved affinity surface is clear and definite.

(p) A detection surface

In view of the amendment of claim 18, the antecedent basis for the detection surface is sufficient.

(q) The orientation

In view of the amendment of claim 23, the antecedent basis for the orientation of the liquid crystal is sufficient.

8. Claim rejections under 35 USC § 103

In the Action claims 1-5, 8-13, 15-20 and 22-23 were rejected under 103(a) as being unpatentable over Bernard et al in view of Abbott et al. Claims 6-7 were rejected under 103(a) as being unpatentable over Bernard et al, in view of Abbott et al as applied to claim 1 and 5 and further in view of Houseman et al. Claim 14 was rejected under 103(a) as being unpatentable over Bernard et al in view of Abbott et al as applied to claims 1 and 12 and further in view of Tang. Claim 21 was rejected under 103 (a) as being unpatentable over Bernard et al in view of

Abbott et al as applied to claim 1 above and further in view of Tarlov et al. Applicant respectfully disagrees for the following reasons:

Bernard *et al.* in view of Abbott *et al.* do not teach each element of the claimed invention. Accordingly, the Examiner has not established a prima facie case of obviousness. Claim limitations may, and often do, read on the prior art, particularly in combination patents. That all elements of an invention may have been old (the normal situation), or some old and some new, or all new, is however, simply irrelevant. Virtually all inventions are combinations and virtually all are combinations of old elements. *Intel Corp. v. United States Int'l Trade Comm'n,* 946 F.2d 821, 842, 20 USPQ2d 1161, 1179 (Fed. Cir. 1991) [Quoting from *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 698, 218 USPQ 865, 870 (Fed. Cir. 1983)]. Furthermore, in order to render a claimed apparatus or method obvious under Section 103, the prior art must enable one skilled in the art to make and use the apparatus or method. Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551 (Fed. Cir. 1989); and Application of Payne, 606 F.2d 303, 314 (CCPA 1979). Bernard et al. provides that one **could fabricate** "smart stamps" with arrayed capturing sites on their surfaces having protein arrays of target molecules. However, Bernard et al do not enable or teach how to make these arrays of proteins. Mere suggestion that the technology may be used for a particular application, without more (i.e. a teaching how to create a plurality of receptors wherein each receptor is independently capable of specifically binding to the ligand where in the presence of the ligand, the receptor specifically binds to the ligand) does not teach one of ordinary skill in the art to practice the invention as recited in claim 1. Accordingly, at least one element of the claimed invention is not taught by the cited combined references, nor any known references. Further, in both cited reference, there is no motivation to combine the references to come upon the recited invention of claim 1.

The detection surface claimed in the invention having a substrate and a liquid crystal may not be considered as an obvious design choice but a synergistic combination such that very minute quantity of ligands may be detected in a sample with accuracy and efficiency. Further the array of receptors allows for numerous ligands to be detected simultaneously using a single affinity substrate, which may then be re-used conveniently as shown in examples of the specification.

Further, there is no motivation to combine the cited references in non-analogous fields, one in the field on microcontact printing and another in the field of molecular interaction visualization. A recent Federal Circuit case explicitly discusses the standards for establishing motivation to combine. (See, In re Lee, 277 F.3d 1338 (Fed. Cir. 2002)). Specifically, the Federal Circuit held that the factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.

Furthermore, an Examiner may not simply rely on conclusory statements even for what they think might be common sense or well known in the art. The 'common knowledge and common sense' on which the Board relied in rejecting Lee's application are not the specialized knowledge and expertise contemplated by the Administrative Procedure Act. Conclusory statements such as those here provided do not fulfill the agency's obligation. This court explained in Zurko, 258 F.3d at 1385, 59 USPQ2d at 1697 that 'deficiencies of the cited references cannot be remedied by the Board's general conclusions about what is 'basic knowledge' or 'common sense.' The Board's findings must extend to all material facts and must be documented on record, lest the 'haze of so-called expertise' acquire insulation from accountability. 'Common knowledge and common sense,' even if assumed to derive from the agency's expertise, do not substitute for authority when the law requires authority.

The Examiner in this case relies on a conclusory statement. Instead of identifying a real reason to combine the references, the Examiner merely cites the claim elements and then states: "Therefore it would have been obvious to one of ordinary skill in the art to employ the method of detecting a ligand of Bernard et al. using the detection surface of Abbott et al. because Abbott et al. teach that liquid crystal detection surfaces do not require labeling of the ligand as was performed in Bernard et al." If anything, this is evidence that Abbott actually teaches away from Bernard et al. Indeed, there is no basis in any of the cited references for combining a paper requiring a radioactive label with a patent teaching label-free detection.

Accordingly, Applicant believes that independent claim 1, and all claims that depend from it, namely clams 2-11 and 13-23 are allowable and a notice regarding the same is respectfully requested.

CONCLUSIONS

It is respectfully submitted that claims 1-11 and 13-23 are in condition for allowance and notice to that effect is earnestly solicited. The Examiner is urged to telephone the undersigned in the event a telephone discussion would be helpful in advancing the prosecution of the present application. The Office is authorized to charge the processing fee or any other surcharges or underpayment, as deemed necessary and appropriate, to the Deposit Account 07-1509 of Godfrey & Kahn, S.C.

Respectfully submitted,

GODFREY & KAHN, S.C.

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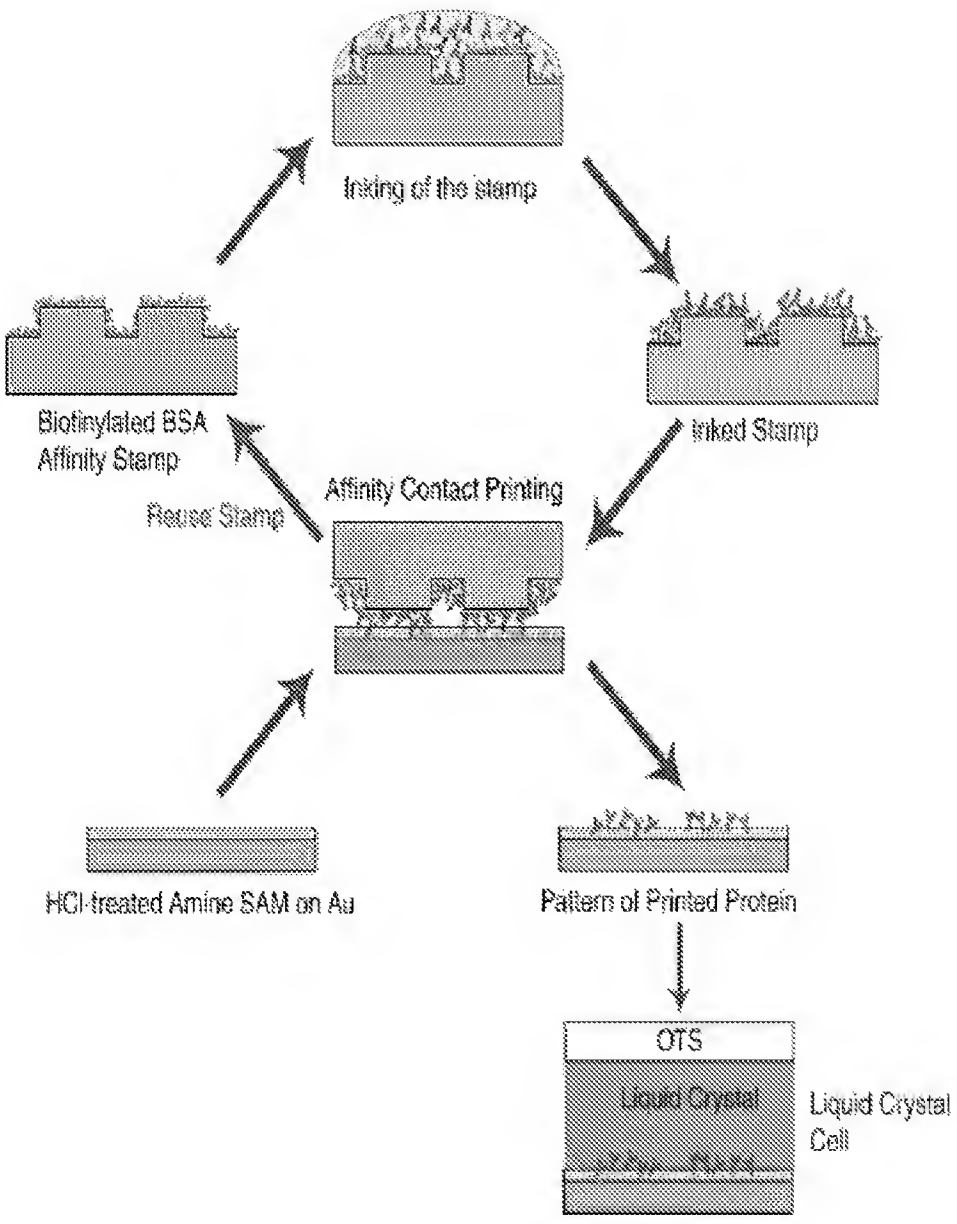
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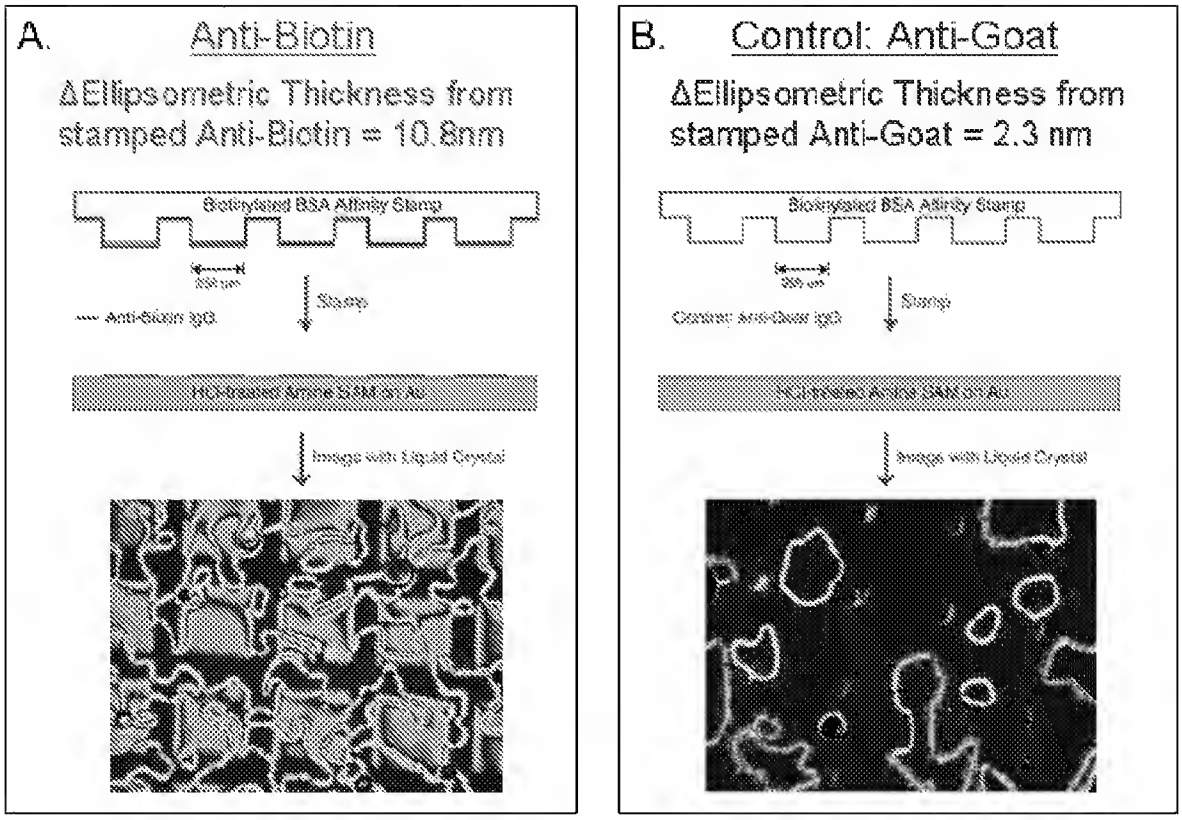
Liquid Crystal
Cell

Figure 1.2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Biotinylated BSA Affinity Stamp
Stamp
Image with Liquid Crystal
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Stamp
Image with Liquid Crystal

Figure 4.2

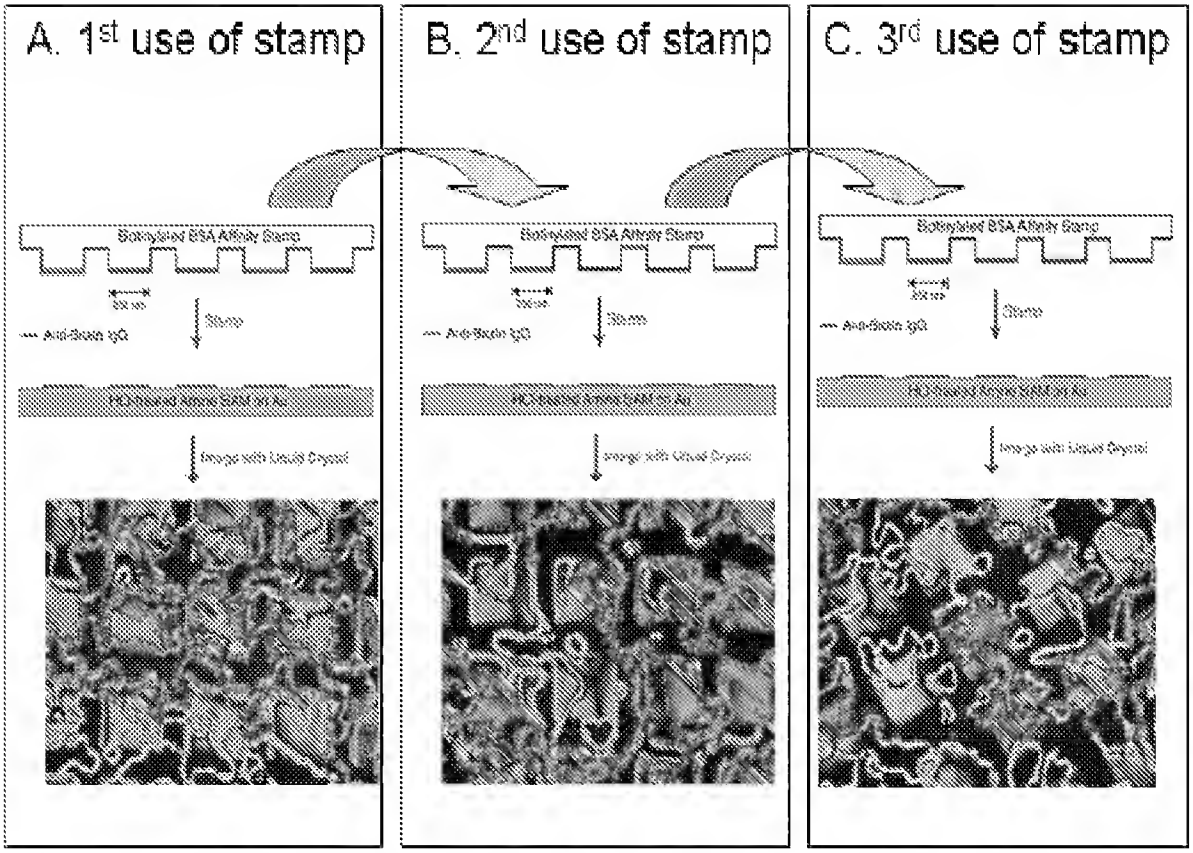

Figure 6.2